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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/392,500	09/09/1999	RONALD TAYLOR	9426-019	1294

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 05/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/392,500	Taylor et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20-24, 26-34, 48-53, 55, 56, and 58-61* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20-24, 26-34, 48-53, 55, 56, and 58-61* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Claim 25 has been canceled. Claims 28 and 52 have been amended. Claims 20-24, 26-34, 48-53, 55, 56 and 58-61 are pending and under consideration.

2. After review and reconsideration, the finality of the Office action of Paper no. 18 is withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 20-24, 26-34, 48-53, 55, 56 and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20, 29, 48, 49, 50, 58, 59 and 60 recite "effective amount of an antibody which specifically binds to C3b(i)". The metes and bounds of the claims are unclear because the claims are lacking a functional limitation by which the "effective amount" can be ascertained, and the specification provides no definition for said "effective amount".

6. Claims 20-22; 24, 26-31, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (U.S. 5,376,356, cited in a previous Office action) as evidenced by Paul (Fundamental Immunology, third edition, 1993, page 926) in view of Kinders et al (U.S. 6,221,621, cited in a previous Office action).

Claim 20 is drawn to a method for detecting cancer comprising administering a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i)covalently linked to a second molecule; waiting for a time interval to permit the labeled antibody to concentrate at any cancerous cite; determining the background level; detecting the labeled antibody at a site in the mammal and determining that cancer is present at said site when the labeled antibody is detected above the background level. Claim 21 is drawn to the method of claim 20 in part, wherein the animal is human. Claims 22, 24 and 28 are drawn to the method of claim 20 in part wherein the labeled antibody is a monoclonal antibody, an antibody labeled with a radioisotope, and administered intravenously. Claim 27 is drawn to the method of claim 20 in part in which the time interval is 6 hours to 48 hours. Claim 28 is drawn to the method of claim 20 in part wherein said method further comprises repeating steps a through e at monthly or yearly intervals.

Claim 29 is drawn to a method for detecting cancer in an animal comprising imaging said animal at a time interval after administration of a labeled antibody which specifically binds to C3b(i) or a labeled antibody which specifically binds to C3b(i)covalently linked to a second molecule;, said time interval being sufficient to permit the labeled antibody to concentrate at any cancerous site in said animal; and determining that cancer is present at said site if the labeled antibody is localized at said site in the animal. Claim 30 is drawn to the method of claim 29 in part wherein the animal is human. Claims 31 and 33 are drawn to the method of claim 29 in part wherein the labeled antibody is a monoclonal antibody, and an antibody labeled with a radioisotope.

Morgan teaches a method for imaging inflammation comprising the intravenous administration of a monoclonal antibody which specifically binds to C3dg (column 14, lines 5-16, column 17, lines 30-50, and column 18, lines 5-7). Morgan teaches that a lapse between 3 and 144 hours is required to allow the labeled recognition agent time to migrate to the target tissue and clear from uninvolved tissue, and that an appropriate time lapse is readily determined by a

person of ordinary skill in the art (column 18, lines 16-25). Morgan teaches that C3dg is a cell or tissue bound activation product of the complement cascade and will be present as a result of complement activation through the classical or alternative pathway (column 14, line 8-11). Paul et al teaches that C3b(i) comprises three peptides linked together by two disulfide bridges and further linked to the target surface (figure 8, panel C). It is evident from Figure 8, panels C and D that C3dg is cleaved off from part of C3bi (figure 8 panels C and D). It is reasonable to conclude that an antibody which specifically binds C3dg will specifically bind C3bi. Further this is acknowledged by Morgan in the statement that C3dg is the final degradation product of C3 (column 14, lines 12-15). Thus Morgan teaches all the limitations of claims 20-22, 24, 26, 27, 29-31, 33 and 34 with the exception of treating cancer, as antibodies which specifically bind C3dg will also specifically bind C3b(i) as the C3dg epitope is within C3b(i) as taught by Paul and by Morgan.

Kinders et al teach a method of detecting cancer comprising the detection of a C3 or a C3 related protein in association with tumors. Kinders et al teaches the that the diagnostic methods may be used to monitor an individual on a periodic basis wherein said individual is at risk for developing cancer or reacquiring cancer, thus fulfilling the specific embodiment of claim 28 with regard to the repetition of the method steps at monthly to yearly intervals (Column 3, line 66 to column 4, line 8). It is noted that claims 20 and 29 comprise the limitation "C3b(i) covalently linked to a second molecule" and thus read on C3 before proteolytic degradation to isolated C3b(i). Kinders et al teach the detection of C3 or C3 related proteins in a cell or tissue sample obtained from patients (column 11, lines 35-43). Kinders et al do not teach the detection of cancer in vivo.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to used the method taught by Morgan for the detection of cancer in vivo. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Kinders on the presence of C3 on tumor cells, and the

teachings of Paul and Morgan et al on the proteolytic degradation of C3 to C3b(i) to C3dg attached to cells. One of skill in the art would know that an antibody which specifically binds C3dg as taught by Morgan, would also specifically bind to C3b(i). The instant claims do not have a limitation wherein the epitope which is bound by the anti-C3b(i) antibody, exclude the fragment which will be proteolytically cleaved off as C3dg. Further, antibodies which specifically bind C3, as taught by Kinders et al to be diagnostic for cancer in in vitro immunoassays also read on the instant invention as claims 20 and 29 comprise the limitation "C3b(i) covalently linked to a second molecule" and thus read on C3 before proteolytic degradation to isolated C3b(i).

7. Claim 20-24, 26-33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (U.S. 5,376,356, cited in a previous Office action) and Paul (Fundamental Immunology, third edition, 1993, page 926) and Kinders et al (U.S. 6,221,621, cited in a previous Office action) as applied to claims 20-22, 24, 26-31, 33 and 34 above, and further in view of Schlom (In: Molecular Foundations of Oncology, pp. 95-133). The limitations and the teachings of the combination of Morgan and Paul and Kinders which render claims 20-22, 24, 26-31, 33 and 34, obvious are set forth above. Claims 23 and 32 are drawn to the methods of claims 20 and 29 in part wherein the labeled antibody is humanized. Neither Morgan nor Kinders teaches a labeled monoclonal antibody which is humanized.

Schlom teaches that humanizing an antibody is preferable to avoid anti-HAMA immune response in cases where the murine antibody or chimeric antibody is administered more than twice (second column second full paragraph of page 98 to line 4 of page 99).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made use humanized anti-C3dg or anti-C3 antibodies for the method of treatment rendered obvious by the combination of Morgan and Paul and Kinders et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom on improvements afforded by the substitution of humanized

antibodies for murine or chimeric antibodies in methods dependent on the multiple administration of antibodies to humans.

8. Claims 20-24, 26-34 55, 56, and 58-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (U.S. 5,376,356, cited in a previous Office action) as evidenced by Paul (Fundamental Immunology, third edition, 1993, page 926) in view of Kinders et al (U.S. 6,221,621 and further in view of Schlom (In: Molecular Foundations of Oncology, pp. 95-133, cited in a previous Office action) as applied to claims 20-22, 24, 26-34 above, and further in view of Paul (pages 922-924) and Xing et al (Cancer Research, 1992, vol. 52, pp. 2310-2317). The limitations of claims, 20-24, 26-33 and 34 and the teachings of Morgan and Paul and Kinders et al which render obvious said claims are set forth above.

Claim 58 is drawn to a method for detecting cancer comprising administering one or more IgM antibodies known to bind to improperly glycosylated cancer cells in a subject; administering an effective amount of a labeled antibody which specifically binds to C3b(i); waiting for a time interval to permit the labeled antibody to concentrate at a cancerous site; determining background level and detecting labeled antibody in the subject wherein the detection of labeled antibody above the background level at a site in the subject is indicative of the presence of cancer at said site. Claim 59 is drawn to a method for detecting cancer comprising administering one or more IgM antibodies known to bind to improperly glycosylated cancer cells in a subject; waiting for a time interval; administering an effective amount of a labeled antibody which specifically binds to C3b(i); waiting for a time interval to permit the labeled antibody to concentrate at a cancerous site; determining background level and detecting labeled antibody in the subject wherein the detection of labeled antibody above the background level at a site in the subject is indicative of the presence of cancer at said site. Claim 60 is drawn to a method for detecting cancer in a subject comprising imaging said subject at a time interval after administration of one or more IgM antibodies now to bind to improperly glycosylated cancer cells and an effective amount of a

labeled antibody to concentrate at any cancerous site is said subject wherein detection of the labeled antibody localized at a site is indicative of cancer at said site. Claim 22, 24 are drawn in part to the methods of claims 58 and 59 wherein the labeled antibody is a monoclonal antibody and labeled with a radioisotope, respectively. Claim 26 is drawn i part to the method of claim 26 wherein the time interval is 6 to 48 hours. Claim 27 is drawn in part to the methods of claims 58 and 59 in which the labeled antibody is administered intravenously. Claims 31 and 33 are drawn in part to the method of claim 60 wherein the labeled antibody is monoclonal and labeled with a radioisotope, respectively. Claim 34 is drawn in part to the method of claim 60 in which the time interval is 6 hours to 48 hours. Claim 55 is drawn in part to the method of claim 58 which further comprises repeating the method steps at monthly intervals. Claim 56 is drawn in part to the method of claim 59 wherein the method steps are repeated at monthly or yearly intervals.

The combination of Morgan and Kinders et al renders obvious claims 22-24, 26, 27, 31-34, 55, 56, and 58-62 with the exception of the administration of one or more IgM antibodies known to bind to improperly glycosylated cancer cells in a subject.

Xing et al teach the BCP7 antibody which specifically binds MUC1 in breast cancer tissue. Xing et al teach that the epitope recognized by BCP7 was masked in native form and exposed in cancer, therefore fulfilling the specific embodiment recited in claims 58-61 drawn to an antibody which specifically binds improperly glycosylated cancer cells in a subject.

Paul et al teach that the initial phase of the complement pathway begins if C1q becomes attached to the Fc portion of an antibody and that in order for the complement cascade to be activated it is necessary for C1q to bind at lest two molecules of IgG1, IgG2, IgG3, but only one molecule of IgM, attached to the target, is necessary for the activation of the complement cascade (page 923, lines 1-4, under the heading "Attachment", page 924, sections 2 and 3, especially second column, lines 6-8).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an IgM antibody that specifically binds an improperly

glycosylated tumor antigen, prior to the administration of the anti-C3dg antibody in a method of detecting cancers rendered obvious by the combination of Morgan and Kinders et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Xing et al on the specificity of an antibody such as BCP4 which recognizes an epitope of Muc1 peptides on breast tumor tissue which is masked in normal breast tissue and the teachings of Paul on the necessity for having an antibody which binds to an antigen i order for the complement cascade to begin, and the further teachings of Paul on the need for only one molecule of IgM versus two molecules of IgG to initiate complement activation. One of skill in the art would be motivated to administer an IgM antibody to insure that complement activation would take place on every cell that bound at least one IgM.

9. Claims 20-24, 26-34, 51, 52, 55, 56, and 58-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (U.S. 5,376,356, cited in a previous Office action) as evidenced by Paul (Fundamental Immunology, third edition, 1993, page 926) in view of Kinders et al (U.S. 6,221,621 and further in view of Schlom (In: Molecular Foundations of Oncology, pp. 95-133, cited in a previous Office action) and Paul (pages 922-924) and Xing et al (Cancer Research, 1992, vol. 52, pp. 2310-2317) as applied to claims 20-24, 26-34 55, 56, and 58-62 above, and further in view of Clark (In: Protein Engineering of antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, Mike Clark, Ed. Page 3-4). The limitations of claims 20-24, 26-34 55, 56, and 58-62 and the teachings of Morgan and Paul and Kinders and Schlom and Xing and Paul which render obvious said claims are set forth above. Claim 51 is drawn in part to the method of claims 58 and 59 in which the labeled antibody is a human antibody. Claim 52 is drawn in part to the method of claim 60 in which the labeled antibody is a human antibody. The combination of references teaches the administration of a humanized antibody; neither Morgan nor Kinders nor Paul nor Schlom nor xing teach the administration of a human antibody.

Clark teaches that an alternative strategy for overcoming HAMA response is to administer human antibodies (page 4, first full paragraph). Clark teaches methods to derive human antibodies in vitro from combinatorial libraries that is less technically difficult than the direct derivation of human antibodies via the Kohler and Milstein technique.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use human antibodies as labeled antibodies in the method rendered obvious by the combination of Morgan and Kinders et al and Paul and Schlom. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Clark and Schlom on the desirability of eliminating the HAMA response by the elimination of antigenic sequences within a rodent antibody and the teachings of Clark on the new methods of isolating human antibodies in vitro by phage display and combinatorial libraries.

10. Claims 20-24, 26-34, 48-53, 55, 56 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (U.S. 5,376,356, cited in a previous Office action) as evidenced by Paul (Fundamental Immunology, third edition, 1993, page 926) in view of Kinders et al (U.S. 6,221,621 and further in view of Schlom (In: Molecular Foundations of Oncology, pp. 95-133, cited in a previous Office action) and Paul (pages 922-924) and Xing et al (Cancer Research, 1992, vol. 52, pp. 2310-2317) and Clark as applied to claims 20-24, 26-34, 51, 52, 55, 56, and 58-62 above, and further in view of Roitt et al (Immunology (text), 3rd edition, 1993, page 13.7).

Claim 48 is drawn to a method of detecting cancer comprising the administration of plasma to an animal; administering an effective amount of an antibody which specifically binds C3b(i); waiting for an interval to permit the labeled antibody to concentrate at a cancerous site; determining the background level and detecting the labeled antibody, wherein detection of the labeled antibody above the background level at a site in the animal indicates the presence of cancer at said site. Claim 49 is drawn to a method of detecting cancer comprising administering plasma to an animal; waiting for a time interval following step a, administering an effective

amount of an antibody which specifically binds C3b(i); waiting for a time interval following step c to permit the labeled antibody to concentrate at a cancerous site; determining background level; and detecting the labeled antibody, wherein detection of the antibody above the background level is indicative of the presence of cancer. Claim 50 is drawn to a method for detecting cancer in an animal comprising imaging said animal after administering sequentially plasma and an effective amount of a labeled antibody which specifically binds to C3b(i) said time interval being sufficient to permit the labeled antibody to concentrate at any cancerous site in said animal wherein detection of the labeled antibody localized at the site is indicative of cancer at said site. Claim 51 is drawn in part to the methods of claims 48 and 49 in which the labeled antibody is a human antibody. Claim 52 is drawn in part to the method of claim 50 in which the labeled antibody is a human antibody. Claim 53 embodies the method of claim 48 or 49 wherein plasma is administered intravenously. Claims 55 and 56 are drawn in part to the methods of claim 48 and 49, respectively, wherein said methods further comprise repeating the method steps at monthly or yearly intervals.

The combination of Morgan and Paul and Kinders et al and Schlom and Xing and Clark render obvious the specific embodiments of claims 20-24, 26-34, 51, 52, 55, 56, and 58-62 for the reasons set forth above. Neither Moran nor Paul nor Kinders et al nor Schlom nor Clark teach the administration of plasma.

Roitt et al teach that the complement system is one of the four major plasma enzyme systems.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer plasma prior to the administration of the anti C3dg antibody in a method to detect cancer in vivo said method rendered obvious by the combination of Morgan and Kinders et al and Paul. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Roitt on the availability of complement proteins in plasma. One of skill in the art would be motivated to provide enough

complement proteins to insure that C3b were covalently linked to the target cell in order to optimize the binding of the anti-C3dg antibody.

11. All other rejections and objections as set forth in Paper No. 18 are withdrawn.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canellá, Ph.D.

Patent Examiner, Group 1642

May 8, 2003